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EXAMINER	
NGUYEN, Q	
ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 03/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/453,234	BUECHLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-45 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-45 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Claim Objections

Claim 17 is objected to because of the following informalities: the term "to produced" on line 4 of the claim is not proper. Additionally, there are two consecutive commas on line 14 of the claim. Appropriate correction is required.

Claim 35 is objected to because of the following informalities: the term "nucleic segment" on line 1 of the claim should be - - nucleic acid segment - -. Appropriate correction is required.

Sequence compliance

The disclosure is objected to because of the following informalities: The specification contains sequence listings. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

For a complete response to this office action, applicant must submit the required material for sequence compliance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a human antibody display library or a human Fab phage display library comprising providing a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes wherein the human genes is free of human lambda light chain genes and wherein there are no more than 40 human VH and more than 40 VL genes, isolating a population of nucleic acids encoding human antibody chains from lymphatic cells of said transgenic mouse, and forming a library of display packages displaying the antibody chains or Fab fragments; a library with recited limitations generated from the same method, does not reasonably provide enablement for other embodiments in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-16 are drawn to a method of producing a human antibody display library comprising providing a nonhuman transgenic animal whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies; isolating a population of nucleic acids encoding human antibody chains from lymphatic cells of the nonhuman transgenic animal; forming a library of display packages displaying the antibody chains, wherein a library member comprises a nucleic acid encoding an antibody chain, and the antibody chain is displayed from the package.

Claims 17-34 are directed to a method of producing a human Fab phage display library, comprising: providing a nonhuman transgenic animal whose genome comprises a plurality of human immunoglobulin gnes that can be expressed to produce a plurality of human antibodies; isolating populations of nucleic acids respectively encoding human antibody heavy chains and human antibody light chains from lymphatic cells of the nonhuman transgenic animal; cloning the populations into multiple copies of a phage display vector to produce a display library, wherein a library member comprises a phage capable of displaying from its outersurface a fusion protein comprising a phage coat protein, a human antibody light chain or human antibody heavy chain, wherein in at least some members, the human antibody heavy or light chain is complexed with a partner human antibody heavy or light chain, the complex forming a Fab fragment to be screened.

Claims 35-45 are directed to a library comprising nucleic acid segments encoding human antibody chains with limitations recited in the claims.

The specification teaches by exemplification the preparation of antibody phage libraries to interleukin 8 using spleen cells harvested from transgenic mice expressing human heavy and kappa light chain transgenes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci, and the mice were immunized with interleukin 8. After subcloning polyclonal Fab populations into expression vectors and electroporation in *E. Coli*, colonies picked off of the 10^9 and 10^{10} affinity cuts were analyzed for binding to IL-8.

The above evidence has been noted and considered. However, the evidence can not be extrapolated to the instantly broadly claimed invention. With respect to the breadth of the method claims encompassing the use of any and all non-human transgenic animal whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies, apart from the the disclosure of transgenic mice expressing human heavy and kappa light chain transgenes in a background homozygous for disruption of the endogenous mouse heavy and kappa light chain loci, the instant specification fails to provide guidance or direction for one of skilled in the art how to make other non-human transgenic animal encompassed by the scope of the claims. When read in light of the specification, it is essential to obtain a non-human transgenic animal whose genome comprises a plurality of human immunoglobulin genes replacing endogenous genes for the production of a plurality of human antibodies in said transgenic animal. At the effective filing date of the present application, the art of transgenesis was known to be highly unpredictable. Particularly, the predictability of an anticipated phenotype arises from the disruption of a

particular gene, for this instance the disruption of endogenous heavy and light chain loci and to be replaced by human immunoglobulin genes. The instant specification teaches the generation of Cμ targeted mice with disrupted non-functional immunoglobulin genes using the ES cell approach (See example 24 on page 89). Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supported phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discussed that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. reported that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph). However, the instant specification fails to teach the production of any knockout animal having a disruption of endogenous immunoglobulin genes other than the disclosed Cμ knockout mice. It is also well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (Moreadith et al., Summary on page 214). Seamark (Reprod. Fertil. Dev. 6:653-657, 1994) supported this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract). Likewise, Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996) stated that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission

of an ES cell has been successfully demonstrated" (column 1, first paragraph, page S38). Given the state of the ES cell technology that supports only the production of transgenic knockout mice, the instant specification fails to provide sufficient guidance or direction for one skilled in the art to make other transgenic non-human mammals lacking functional endogenous immunoglobulin genes using the ES cell approach. Additionally, the instant specification fails to provide sufficient guidance or direction for one skilled in the art how to make a non-human transgenic animal whose genome comprises a plurality of human immunoglobulin genes other than the disclosed transgenic mice whose genome comprises human immunoglobulin genes that are free of the human lambda light chain gene, and wherein there are no more than 40 VH genes and no more than 40 VL genes. Mullins et al. (J. Clin. Invest. 98:S37-S40) noted that the randomly integration of exogenous DNA into chromosomal DNA is a major problem for pronuclear microinjection method, the same approach that transgenic mice were generated in the instant application. Positional effects, arisen from the randomly incorporation of exogenous DNA, can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene (column 2, first paragraph, page S37). Because of the unpredictable nature of random transgene integration and positional effects, it would be extremely difficult to predict successful human immunoglobulin gene transfer in all other animal species, such that a plurality of human antibodies could be produced in such transgenic animals. Mullins et al. further stated that "the suitability of a particular species for the specific questions being

addressed, bearing in mind that a given construct may react very differently from one species to another." (column 1, second paragraph, page S39). With the lack of such guidance, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and use the instantly broadly claimed invention.

With respect to claims drawn to libraries having the recited characteristics, particular for ones wherein library members exhibit binding affinity of at least 10^9 M^{-1} or greater to a specific target, the instant specification fails to provide specific parameters or conditions used to establish such libraries other than those of the method claimed in the present application. Moreover, Kucherlapati et al. (WO 96/33735) have noted that it has been difficult to isolate or obtain high affinity antibodies to human proteins, and that the approach utilizing the combination of phage display technology with the Xenomouse, similar in nature to the claimed method of the present invention, offers an advantage over other known methods for obtaining high affinity human antibodies (page 13, lines 1-7). Given the lack of sufficient guidance or direction provided by the instant specification regarding to the making of libraries having recited characteristics by approaches other than by the claimed method of the present application, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the broadly claimed invention.

In summary, due to the lack of direction or guidance provided by the specification, the unpredictability of the transgenesis art, and the breadth of the claims,

it would have required undue experimentation without a predictable degree of success for one skilled in the art to make and use the broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 5, 9, 23 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 2, it is unclear what is encompassed by the term "linked to" in the claim. Is it a chemical or physical linkage? Since the term is not defined in the specification, the metes and bounds of the claim can not be clearly determined.

Claim 4 recites the limitation "phage display vector" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 recites the limitation "the display vector" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

In claim 9, the phrase "library members displaying an antibody chain and binding partner (if present) with specific affinity for the target bind to the target, and separating antibody chains bound to the target to produce a subpopulation of display packages" is unclear and it renders the claim indefinite. Should library members must display both antibody chains including the appropriate binding partner to bind specifically to their target? Then, what does the phrase "(if present)" mean? Furthermore, library members displaying antibody chains bound to the target are separated to produce a

subpopulation of display packages, not antibody chains bound to the target. Clarification is needed.

Claim 23 recites the limitation "from the sublibrary" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim.

In claim 43, it is unclear what is encompassed by the term "and/or" and therefore it renders the claim indefinite. Does each segment comprise sequence(s) from a human VH or human VL gene or both genes. Which situation? The metes and bounds of the claim can not be determined clearly. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Burton et al. (Proc. Natl. Acad. Sci. USA 88:10134-10137, 1991).

The claims are drawn to a library of at least ten different nucleic acid segments encoding human antibody chains, wherein at least 50% of segments in the library encode human antibody chains showing at least 10^8 M^{-1} affinity for the same target and no library member constitutes more than 50% of the library, and the same wherein the library comprises at least ten pairs of different nucleic acid segments, the members of a pair respectively encoding heavy and light human antibody chains, wherein at least 50%

of the pairs encode heavy and light human antibody chains that form complexes showing specific affinity for the same target, and no pair of nucleic acid segments constitutes more than 50% of the library.

Burton et al. disclose a randomn combinatorial phage library from which 40 representative *E. Coli* clones comprising the DNA encoding human Fab fragments reactive against the surface glycoprotein gp120 of type 1 human immunodeficiency virus were grown up and screened. The supernatants of 33 clones showed clear reactivity. Sequencing analysis of DNA samples from the reactive 33 clones revealed at least 10 clones having unique heavy chains and 20 clones having unique light chains (See page 10136, column 2, and Fig. 1). Additionally, most of the secreted Fab fragments have binding constants at least $10^8\ M^{-1}$ for gp120 (See page 1036, column 2, second last paragraph). Therefore, the reference clearly anticipates the instant claimed invention.

Claims 35-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Gray et al. (WO 98/47343 with a published date of October 29, 1998).

The claims are drawn to a library of at least ten different nucleic acid segments encoding human antibody chains, wherein at least 50% of segments in the library encode human antibody chains showing at least $10^8\ M^{-1}$ affinity for the same target and no library member constitutes more than 50% of the library; and the same wherein the library comprises at least ten pairs of different nucleic acid segments, the members of a pair respectively encoding heavy and light human antibody chains, wherein at least 50%

of the pairs encode heavy and light human antibody chains that form complexes showing specific affinity for the same target, and no pair of nucleic acid segments constitutes more than 50% of the library. Claims 37 and 38 are drawn to the libray of claim 36 wherein the library comprises at least 100 pairs and 1000 pairs of different nucleic acid segments, respectively.

With regarding to the library encode human antibody chains showing at least 10^8 M^{-1} affinity for the same target, Gray et al. teach a method for preparing a library of replicable genetic packages displaying from their outersurface polypeptides including antibodies, particularly Fab fragments (page 3, lines 20-27). Additionally, Gray et al. further teach that the disclosed library comprises at least four different nucleic acid segments, at least 90% of segments in the library encode polypeptides showing specific affinity for a target and no library member constitutes more than 50% of the library. In some libraries, at least 95% of library members encode polypeptides having specific affinity for a target and such libraries have at least 4, 10, 20, 50, 100, 1000, 10,000 or 100,000 different coding sequences, and no member constitutes more than 50%, 25% or 10% of the total coding sequences in the library (page 5, lines 29-37 and page 28, lines 24-28). As defined by Gray et al., specific binding between an antibody and an antigen means a binding affinity of at least 10^6 M^{-1}, and more preferably 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1} or 10^{10} M^{-1} (page 8, second last paragraph). Therefore, the reference clearly anticipates the instant claimed invention.

It should be noted that Buechler et al. (U.S. Patent No. 6,057,098 with an effective filing date of April 04, 1997) disclosed the same teachings as Gray et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 98/47343 with a published date of October 29, 1998) or Buechler et al. (U.S. Patent No. 6,057,098 with an effective filing date of April 04, 1997) in view of Kucherlapati et al. (WO 96/33735 with a published date of October 31, 1996, IDS, AS) and Lonberg et al. (U.S. Patent No. 5,770,429 with the effective filing date of October 10, 1995; IDS, AD).

Claims 1-16 are drawn to a method of producing a human antibody display library comprising providing a nonhuman transgenic animal whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies; isolating a population of nucleic acids encoding human antibody chains from lymphatic cells of the nonhuman transgenic animal; forming a library of display packages displaying the antibody chains, wherein a library member comprises a nucleic acid encoding an antibody chain, and the antibody chain is displayed from the package.

Claims 17-34 are directed to a method of producing a human Fab phage display library, comprising: providing a nonhuman transgenic animal whose genome comprises a plurality of human immunoglobulin gnes that can be expressed to produce a plurality of human antibodies; isolating populations of nucleic acids respectively encoding human antibody heavy chains and human antibody light chains from lymphatic cells of the nonhuman transgenic animal; cloning the populations into multiple copies of a phage display vector to produce a display library, wherein a library member comprises a phage capable of displaying from its outersurface a fusion protein comprising a phage coat protein, a human antibody light chain or human antibody heavy chain, wherein in at least some members, the human antibody heavy or light chain is complexed with a partner human antibody heavy or light chain, the complex forming a Fab fragment to be screened.

Claims 35-45 are directed to a library comprising nucleic acid segments encoding human antibody chains with limitations recited in the claims.

With respect to the enabled scope of the instant claims as set forth previously, Gray et al. teach a method for preparing a library of replicable genetic packages displaying from their outersurface polypeptides including antibodies, particularly Fab fragments (page 3, lines 20-27). A library member comprises a phage displaying from its outer surface a fusion protein comprising a phage coat protein, an antibody light chain or heavy chain variable domain and a tag. In at least some members, the antibody heavy or light chain is complexed with a partner antibody heavy or light chain variable domain chain, the complex forming a Fab fragment to be screened. The fusion protein and/or the partner antibody heavy or light chain are encoded by segment(s) of the genome of the phage. A tag is also fused to either the fusion protein or the partner antibody heavy or light chain, and the tag is the same in different library members. The number of copies of the fusion protein and the partner antibody chain displayed per phage vary between library members (page 4, lines 8-21). The antibody encoding sequences can be obtained from lymphatic cells of a human or nonhuman animal, usually the cells have been immunized, in which case immunization is performed *in vivo* before harvesting the cells or *in vitro* after harvesting the cells, or both, and often spleen cells of an immunized animal are a preferred source of material (page 18, lines 22-27). Gray et al further teach that the library or a fraction of thereof is contacted with a receptor having a specific affinity for the tag under conditions whereby library members displaying at least two copies of the fusion protein are preferentially bound to immobilized receptor by multivalent bonds between the receptor and the at least two copies of the tag. Library members bound to the receptor are then separated

from unbound library members to produce a sublibrary enriched relative to the library for members displaying at least two copies of the fusion protein (page 4, lines 21-30). Additionally, a polyvalent phage display library can be further screened by contacting the library with a target lacking specific affinity for the tag moiety and separating library members bound to the target via their displayed polypeptides from unbound library members. DNA segments encoding polypeptides having specific affinity for a target can be subcloned in an expression vector, and the polypeptides expressed in host cells (page 5, lines 17-24). Gray et al. further teach that the disclosed library comprises at least four different nucleic acid segments, at least 90% of segments in the library encode polypeptides showing specific affinity for a target and no library member constitutes more than 50% of the library. In some libraries, at least 95% of library members encode polypeptides having specific affinity for a target and such libraries have at least 4, 10, 20, 50, 100, 1000, 10,000 or 100,000 different coding sequences, and no member constitutes more than 50%, 25% or 10% of the total coding sequences in the library (page 5, lines 29-37 and page 28, lines 24-28). As defined by Gray et al., specific binding between an antibody and an antigen means a binding affinity of at least 10^6 M^{-1}, and more preferably 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1} or 10^{10} M^{-1} (page 8, second last paragraph). Buechler et al. teach essentially the same as Gray et al.

However, neither Gray et al. nor Buechler et al. disclose a method of producing a human antibody display library or a human Fab phage display library using isolated populations of nucleic acids from lymphatic cells of a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce

a plurality of human antibodies. Nor do the references teach the same method wherein the nucleic acids encode variable regions of the antibody chains and the display vector comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region, or wherein the plurality of human genes is free of human lambda light chain genes or wherein there are no more than 40 human VH or VL genes included in the plurality of human genes. With regarding to claims directed to a library in which library members encode heavy and light human antibody chains having specific affinity at least 10^9 M^{-1} or 10^{10} M^{-1} for a target, neither references clearly demonstrates that such a library was obtainable.

Kucherlapati et al. teach that the genes encoding the repertoire of immunoglobulins produced by the immunized animal can be used to generate a library of immunoglobulins to permit screening for those variable regions which provide the desired affinity using the phage display techniques (page 11, lines 15-37). Clones from the library which have the desired characteristics can then be used as a source of nucleotide sequences encoding the desired variable regions for further manipulation to generate antibodies or analogs with these characteristics using standard recombinant techniques (page 3, lines 6-15). One such immunized animal is a transgenic XenoMouse, being immunized with a desired antigen, and wherein said transgenic mouse is substantially incapable of producing endogenous heavy or light immunoglobulin chain, but capable of producing immunoglobulins with both human variable and constant regions (page 2, lines 10-15 and lines 22-31). In the Xenomouse,

the human heavy chain YAC, yH1C comprising of 870 kb of the human variable region, the entire D and J_H region, human μ, δ, and $\gamma 2$ constant regions and the mouse 3' enchancer; and human light chain YAC, yK2 comprising of 650 kb of the human kappa chain proximal variable region (V_κ), the entire J_κ region, and C_κ with its flanking sequences that contain the kappa deleting element are used (page 6, lines 1-8). Moreover, Kucherlapati et al. disclose that the genes encoding antibodies can be prepared from primary B cells of the blood or lymphoid tissue (spleen, tonsils, lymph nodes, bone marrow) of the immunized animal (page 3, lines 1-3). Kucherlapati et al. further teach that the combination of phage display technology with the XenoMouse offers a significant advantage over previous applications of phage display in obtaining high affinity antibodies to human proteins via somatic mutation by repeated immunizing the XenoMouse with human proteins (page 13, lines 1-7).

Apart from the Xenomouse, Lonberg et al. disclose another transgenic mouse comprising an inactivated endogenouse mouse immunoglobulin gene locus, and said transgenic mouse further containing in its genome transgenes comprising a 670 to 830 kb human genomic heavy chain fragment containing members of all six of the known V_H families, the D and J gene segments, as well as the μ, δ, $\gamma 3$, $\gamma 1$ and $\alpha 1$ constant regions (column 30, lines 9-20); and a human genomic light chain 450 kb fragment or in combination with another genomic 400 kb fragment containing all of C_κ, the 3' enhancer, all J segments and at least five to at least 20 different V segments (column 53, lines 40-67). Lonberg et al. also noted that human heavy chain locus is estimated to consist of approaximately 200 V gene segments (current data supports the existence of

about 50-100 V gene segments) spanning 2 Mb (column 29, lines 65-67). Lonberg et al. further teach that a hybridoma composed of a B cell obtained from the disclosed transgenic mouse produces an immunoglobulin having a binding constant of at least 10^{10} M^{-1} for binding to a predetermined human antigen (See the claims).

Accordingly, at the time of the instant invention it would have been obvious to the ordinary skilled artisan to modify the method for preparing a library of replicable genetic packages displaying from their outersurface polypeptides including antibodies, particularly Fab fragments taught by Gray et al. by using antibody encoding sequences obtained from lymphatic cells of the XenoMouse as taught by Kucherlapati et al. or from lymphatic cells of the transgenic mouse disclosed by Lonberg et al. to arrive at the instant claimed invention. One of ordinary skilled artisan would have been motivated to carry out the modification because as mentioned above Kucherlapati teach that the combination of phage display technology with a transgenic mouse such as the XenoMouse offers a significant advantage over previous applications of phage display for obtaining high affinity antibodies (e.g. those with 10^{9} M^{-1} or 10^{10} M^{-1} affinity) to any human protein via somatic mutation by repeated immunizing the XenoMouse with human proteins (page 13, lines 1-7). It would be unethical and impossible to administer repeatedly into a human any and all desired antigen or normal human proteins to generate high affinity antibodies against the desired antigen or normal human proteins. One of ordinary skilled in the art would have a predicted expectation of success for the modified method in view of the combined teachings of Gray et al., Kucherlapati et al. and Lonberg et al. With regard to recited method steps wherein the nucleic acids

encode variable regions of the antibody chains and the display vector comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region, these are standard molecular biology techniques and would have been within the scope of skills of the ordinary artisan at the time of the instant invention. The claimed library of the instant invention would also become obvious to one of ordinary skilled artisan because the method for making a library having recited limitations is obvious for reasons cited above.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Dave Nguyen
Primary Examiner
AU 1633

Quang Nguyen, Ph.D.